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# A novel iloprost administration method with portable syringe pump for the treatment of acral ulcers and Raynaud's phenomenon in systemic sclerosis patients. A pilot study (ILOPORTA)

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**Key words:** systemic sclerosis, Raynaud's phenomenon, skin ulcers, infusion pumps, iloprost, home treatment

## ABSTRACT

**Objective.** *The objective of the study is to evaluate the feasibility, safety and efficacy of home infusion of iloprost with the new portable syringe pump Infonde<sup>®</sup>, for the treatment of scleroderma-related Raynaud's phenomenon and digital ulcers.*

**Methods.** *12 scleroderma patients were treated with iloprost at home, using the pump, with infusion cycles of 2 days per month (24 hours a day), for 6 months.*

**Results.** *The home treatment proved feasible since ten patients (83%) completed the entire infusion cycle, thus satisfying the feasibility target imposed by the protocol (75%). Side effects related to the device or venous access occurred in 3 out of 65 total 48-hour infusions (4.6%). They mostly consisted in phlebitis. No adverse events related to the device management were reported.*

*Among the ten patients who completed the infusions, three showed a reduction in the number of ulcers, three maintained the same number, and four had no ulcers throughout the observation period.*

*Patient's perception of their quality of life and wellness during home infusions, expressed with the Visual Analogue Scale (VAS) improved from 79/100 at the first infusion to 91/100 at the end of the study. All patients expressed a positive global judgment regarding this innovative method of iloprost infusion.*

**Conclusion.** *The infusion of iloprost at home with Infonde<sup>®</sup> is feasible, safe and effective. Moreover, this approach presents potential advantages from the economic and organisational point of view. Because of the pilot design of our study, these results need to be confirmed in larger randomised trials.*

## Introduction

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterised by microangiopathy, increased deposition of extracellular matrix with progressive fibrosis, both in the skin and in visceral organs that can involve lungs, heart, kidneys, and gastrointestinal tract (1).

SSc vascular disease involves vessels with luminal occlusion, thrombosis, and vasospasm. Complex interactions between endothelial cells, vascular smooth muscle cells, extracellular matrix and circulating mediators contribute to vascular remodelling, vasospasm, and vessel occlusion (1-2). Raynaud's phenomenon (RP) and digital ulcers (DU) are the main clinical features of vascular involvement.

Among the different medical strategies which have been attempted, intravenous iloprost was demonstrated to be effective in the treatment of RP secondary to scleroderma at decreasing the frequency and the severity of attacks and preventing or healing digital ulcers (3-7).

Nowadays, iloprost infusion is recommended by European League Against Rheumatism (EULAR) guidelines for the treatment of SSc for the treatment of SSc-related digital vasculopathy to reduce the frequency and severity of SSc-RP attacks and to heal active digital ulcers in patients with SSc (8).

The standard therapeutic protocol consists in intravenous administration by peristaltic pump or syringe pump (0.5-2 ng/kg/min) according to the protocol used in the approval study (6), although data from the literature also support the use of a simple flow device (9, 10). It should be administered in an inpatient or in an outpatient hospital setting, every 30-45 days depending on the clini-

Competing interests: none declared.

cal condition of patients. The hospital setting is required to guarantee safety during intravenous infusion due to the common side effects (most commonly headache, nausea, low blood pressure, fatigue and flushing). Furthermore, the most commonly used high-speed infusion scheme can lead to an even poorer drug tolerance. Nevertheless, low dose iloprost was shown to be equally effective as high-dose in long-term treatment and was clearly better tolerated (11) and there is not a single accepted protocol, with various published infusion schemes that are effective and tolerated (6, 7, 11-15).

An important issue about iloprost therapy is that its administration may be limited by difficulty for patients to reach the hospital, contributing to treatment discontinuation. Finally, costs due to hospital iloprost infusion represent a non-neglectable issue.

Recently, different novel portable devices for infusion therapy have become available on the market, e.g. elastomeric pumps and the portable syringe pump Infonde® (Italfarmaco S.p.A., Milan, Italy), but only the latter has been approved for administration of iloprost. Previous studies have shown that treatment with Infonde® is better appreciated by patients and medical staff compared to traditional methods (16, 17). Also, a Health Technology Assessment has demonstrated that use of the device promotes an improvement in the organisation of the medical department and a reduction of the total costs of treatment (18), but always in hospital settings.

We assumed that a continuous low-rate infusion could be well tolerated and safe to be practiced at home, with benefits for patients in terms of acceptance and quality of life, and benefits for medical structures in terms of reducing overcrowding, guaranteeing a regular administration of therapy and finally, economic savings. We performed a pilot study to evaluate the use of the portable syringe pump Infonde® for iloprost home infusion.

## Methods

We carried out a pilot open-label study at Ancona Ospedali Riuniti University

Hospital, Italy, EUDRACT code 2013-004596-12. The study was performed in winter, between October 2014 and April 2015 when RP and vascular complications are maximally expressed.

## Patients

The study population was made up of voluntary patients affected by systemic sclerosis and secondary RP treated at the Clinica Medica Centre of the Università Politecnica delle Marche, Italy.

The study inclusion criteria were: presence of acral ulcers and/or RP secondary to SSc, adequate venous access (assessed by selected nurses) or central venous access, aged between 18 and 80, and mandatory contraception for women of childbearing age throughout the experimental period.

The study exclusion criteria were: hypersensitivity to iloprost or to any of the excipients, pregnancy, lactation, severe coronary heart disease or unstable angina, myocardial infarction in the previous six months, acute or chronic congestive heart failure (NYHA II-IV), severe arrhythmias relevant to the prognosis, suspected pulmonary congestion, cerebrovascular events in the last three months, chronic renal failure (GFR <30 ml/min), liver cirrhosis, treatment with vasodilators (calcium-channel blockers, nitroprusside sodium, minoxidil, etc.), endothelin receptor antagonists and phosphodiesterase-5 inhibitors, active gastrointestinal, genito-urinary or respiratory bleeding, cerebrovascular haemorrhage, cerebral aneurysm, dissecting aortic aneurysm, bacterial endocarditis, surgery performed in the previous three months or scheduled central nervous system or eye surgery or trauma associated with large exposed wounds, severe thrombocytopenia (PLT <20000/mm<sup>3</sup>), severe anaemia (Hb <8 g/dl), severe uncontrolled hypertension, orthostatic hypotension, history of cephalgia and/or chronic dizziness diagnosed by a specialist and/or for which the patient is on treatment, and acute gastrointestinal disease.

## Procedure for home infusion

The device used for home administra-

tion of iloprost was the portable pump Infonde® (Italfarmaco S.p.A., Milan, Italy), with a 25.5 ml disposable reservoir, able to administer micro doses of 7.44 µl at adjustable intervals. The total weight of the device is 118 grams (battery included). The infusion speed is adjustable from a minimum of 0.6 ml/h to a maximum of 9 ml/h. It can be placed around the neck or on the belt, allowing ample mobility and normal day-to-day activities during the infusion. The infusion scheme consisted of one vial of iloprost (a vial of 0.5 ml of solution contains 67 µg of iloprost trometamol, equivalent to 50 µg of iloprost) diluted in saline solution, for a total volume of 25.5 ml, administered over 24 hours through the portable syringe pump. The infusion speed was 1.05 ml/h. This infusion scheme was repeated for two consecutive days, every four weeks, for six months. After the final infusion, there was a final meeting between the patient and the medical team.

Before any infusion, all the patients underwent general medical examination, standard blood checks (complete blood count and renal function) and an electrocardiogram. The number of events and the evolution of any acral ulcer were recorded, and advanced medications were prescribed when necessary. Patients were trained by investigators to use the syringe pump and to manage a possible malfunction of the device.

After the infusion started, patients were observed for two hours and then they were free to go home.

After 24 hours, at the end of the first vial, patients had to come back to our department for the second vial infusion. At the second day visit, physicians checked patient's blood pressure and asked about adverse events: if there were no contraindications, the syringe pump was loaded with the second vial of iloprost, at the same dilution and speed with an observation period of one hour. At the end of the infusion, the pump was disconnected and the cannula removed. Adverse events were investigated and recorded and blood pressure was checked again.

If no side effects occurred during the previous infusions, the observation pe-

riod was reduced respectively to one hour after the beginning of the first vial and thirty minutes after the second.

#### Endpoints and evaluations

The primary end-points of the study were:

- **Feasibility**, measured by the percentage of patients who completed the entire infusion cycle (2 infusions/month for 6 months). In previous similar trials (6, 11, 12, 15) the drop-out rate was between 15% and 35%, thus we considered a minimum percentage of 75% of patients completing the study as index of feasibility;
- **Safety**, considering the total number and type of home-reported adverse events related to the management of the device, of the peripheral venous access or directly related to the drug administration.

The secondary endpoints were:

- **Efficacy** on RP and acral ulcers, evaluated through a quantitative analysis of vasospastic events (frequency and duration) and considering the evolution of acral ulcers in the observational period.
- The impact of this new treatment method on the *patients' quality of life*, assessed through the EuroQol Quality of life scale (EQ-5D) (19) at T0 (first infusion), T3 (fourth infusion) and T6 (control).

We used three different dedicated forms to assess acral ulcers, RP and patient's quality of life respectively. In the first, we recorded the number of ulcers over time and, in particular, the difference in count from T6 to T0, as well as qualitative features of the ulcers.

The second form was provided monthly to each patient to record the number of events and the duration of RP as well as the grade of discomfort caused by each episode; these parameters were analysed from T0 to T6.

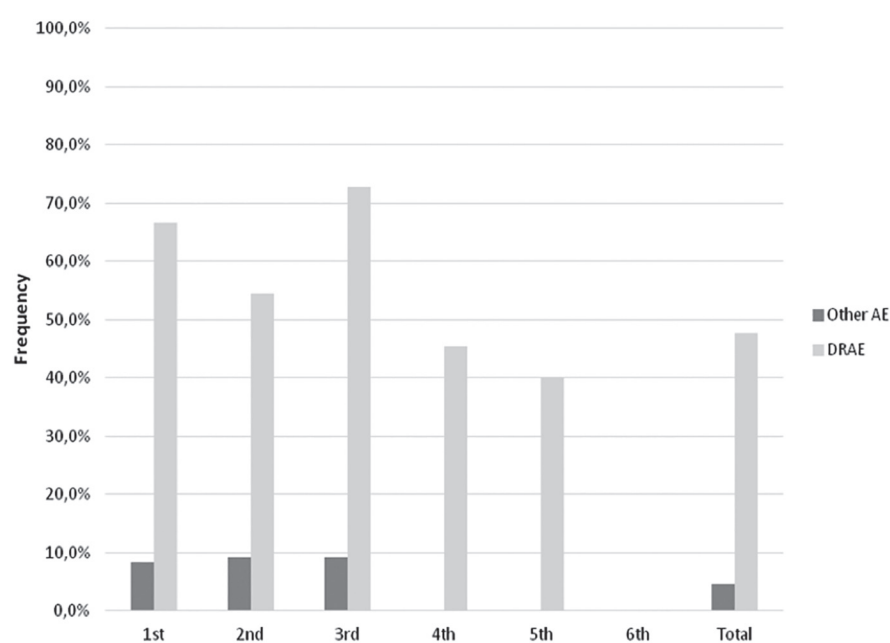
The last form was represented by the EQ-5D, made up of a visual analogue scale regarding the personal state of health and of a multiple choice test regarding different day-to-day activities. The whole form was completed at T0, T3, T6 (1st, 4th infusions and control) while the second one was completed before each infusion.

**Table I.** Study population characteristics.

Median age (Minimum - Maximum) [years]	53 (30 - 72)
Male/Female (%)	3 (25%) / 9 (75%)
Mean disease duration (Minimum - Maximum) [months]	118 (15 - 309)
Limited/Diffuse SSc * (%)	5 (42%) / 7 (58%)

\*SSc: scleroderma.

Limited form and diffuse form of scleroderma according to LeRoy Classification [LeRoy EC, et al.: Scleroderma (systemic sclerosis): Classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-205].



**Fig. 1.** Adverse events frequency divided into drug-related events (DRAE) and administration/device malfunction events (Other AE).

#### Data analysis

The present study is a pilot study exploring feasibility and safety, so no comparison group was required. Data collected in paper forms were inserted into a Microsoft Excel dataset, and analysed using simple descriptive statistics.

#### Human rights

The study was approved by the local ethics committee and received the EUDRACT code 2013-004596-12. The medication and device were used off-label due to the infusion method. Signed informed consent was requested for enrolment. The study was performed in accordance with the Declaration of Helsinki.

#### Results

We enrolled 12 patients, 3 men and 9 women that satisfied the inclusion criteria. In Table I the demographic and

clinical characteristics of our study population are described.

Results about feasibility and safety also include the data relative to patients who withdrew from the study. Results about efficacy and quality of life are relative to the patients who completed the study.

#### Feasibility

The initial study cohort was composed of twelve patients. Two of them withdrew from the study: the former because of worsening of his clinical conditions and the latter because of poor tolerance to the infusion therapy. Ten patients (83%) completed the study, thus satisfying the feasibility target imposed by the protocol.

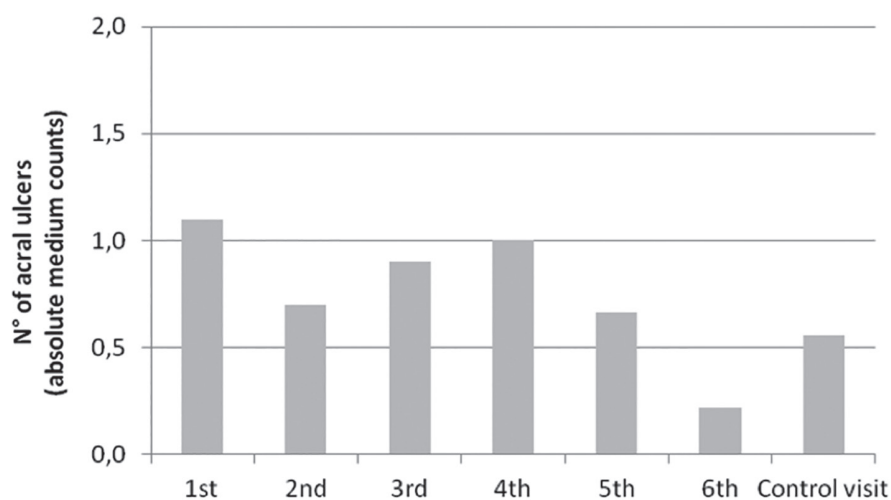
#### Safety

Side effects related to the device or venous access occurred in 3 out of 65

**Table II.** Common and uncommon adverse event reported. Only one patient dropped out from the study for drug intolerance.

Adverse event	No. of patients (%)	No. of episodes	% on the total no. of infusion
Headache	9 (75)	27	41.5
Nausea	5 (41.7)	8	12.3
Arthralgia	2 (16.7)	2	3.1
Fatigue	2 (16.7)	2	3.1
Dizziness	2 (16.7)	2	3.1
Face tension	1 (8.3)	1	1.5
Flushing	1 (8.3)	1	1.5
Vertigo	1 (8.3)	1	1.5
Mild hand oedema	1 (8.3)	1	1.5
Hands pain	1 (8.3)	1	1.5
Hypotension*	1 (8.3)	1	1.5
Inferior limbs paraesthesia	1 (8.3)	1	1.5
No adverse events	1 (8.3)	-	-

\*Hypotension was due to an inappropriate drug administration.



**Fig. 2.** The trend on the acral ulcers medium counts shows a global slight reduction, also confirmed at the control visit.

total 48-hour infusions (4.6%). They mostly consisted in phlebitis. No adverse events related to device management were reported. Drug-related adverse events were reported in 31 (47.7%) among the total infusions, decreasing from the first to the last infusion (Fig. 1).

As shown in Table II, the most frequent side effects were headache (41.5% of the infusions), mostly mild and not interfering with day-to-day activities (patients resorted to paracetamol in only two cases) and nausea (12.3% of the infusions). Less common adverse events were arthralgia (3.1%), fatigue (3.1%), dizziness (3.1%), and hand oedema (1.5%). A single episode of hypotension (1.5%) was reported and it was due to a small amount of Iloprost (left in the in-

fusion tube) rapidly infused during the PORT-cath washing with saline solution. The intensity of the adverse events was mild, except for a case of intense headache, dizziness, nausea and paresthesia which caused the withdrawal of the patient from the study.

*Efficacy*

Efficacy data refer only to ten patients because of the difficulty to enrol all the twenty patients that were initially expected, therefore the evaluation of efficacy is only descriptive.

*Acral ulcers*

Among the ten patients who concluded the infusions, three had a reduction of the number of ulcers, three maintained the same number, and four had no ulcers

throughout the observation period (Fig. 2). Of note, the three patients who had a decrease in the number of ulcers were the ones with a more severe disease and a higher initial number of ulcers.

The patients who had no ulcers at all throughout the six months of the study, had probably benefited from iloprost's therapeutic effects, considering that they had anamnestic evidence of acral ulcers during the previous cold seasons.

*Raynaud's phenomenon*

The global number of RP attacks per month for each single patient increased in the first four infusions (n=30; n=32; n=67; n=77) to progressively reduce afterwards (n=61; n=46; n=47), in accordance with the temperature trend. The mean duration of each single attack remained quite stable during the different infusions, with an average value that became three/four times lower after the last infusion (Fig. 3).

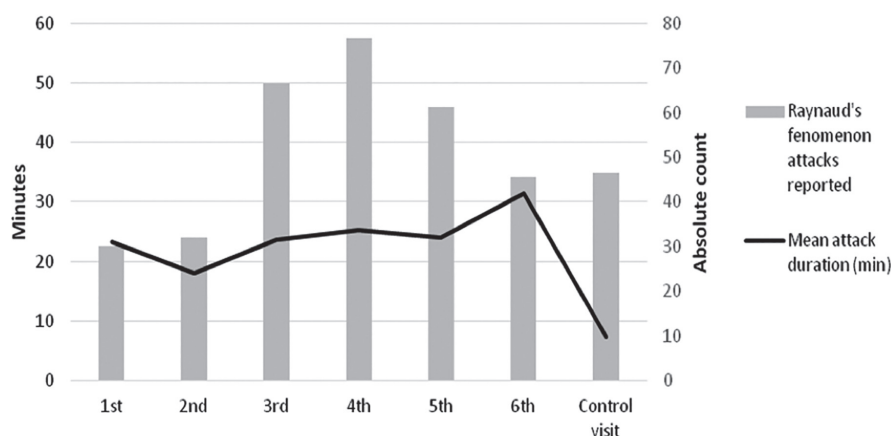
*Patients' quality of life and satisfaction*

Patients' quality of life remained stable throughout the observational period (0.7 as medium value in EQ-5D), rising in the last control (0.8), despite a worsening of Raynaud's phenomenon and of acral ulcers due to temperature decrease. However, patients' perception of their quality of life and wellness during home infusions, expressed with the visual analogue scale (VAS), improved from 79/100 at the first infusion to 91/100 at control (Fig. 4)

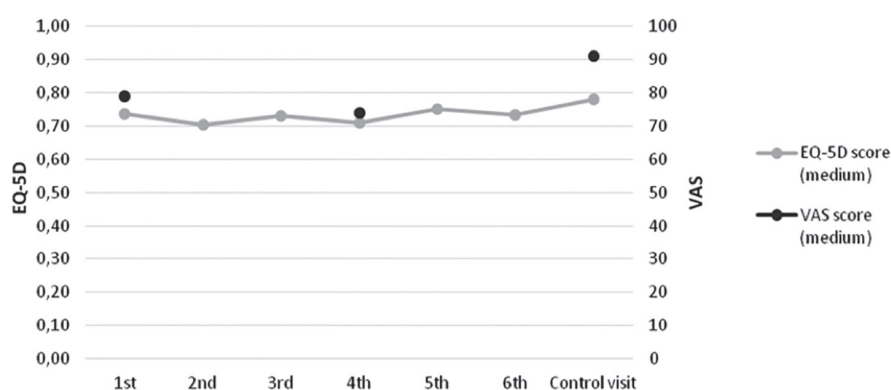
At the end of the present study, all patients expressed a positive global judgment regarding this innovative method of iloprost infusion.

*Economic considerations*

In the context of the current study, represented by the Italian public-health system, the treatment costs were covered by the Outpatient Hospital service, permitting a significant total saving compared to the cost of hospitalisation. Furthermore, the possibility to treat patients at home has freed up human, economic and logistical resources to treat other patients, with an overall optimisation of the activities of our department.



**Fig. 3.** The mean duration of each single attack remained quite stable during the different infusions, while the number of total attacks increased in the months of January and February, according to the climate changes.



**Fig. 4.** Quality of life. EQ-5D: EuroQol quality of life scale; VAS: visual analogue scale.

## Discussion

Systemic sclerosis is a connective tissue disease characterised by fibrosis and vascular phenomena that frequently affect the skin and other organs. About 90% of the patients with SSc suffer from secondary RP, which is usually severe and accompanied by digital ischaemic ulcers that carry the risk of infection and amputation. Iloprost is a synthetic prostacyclin analogue with vasodilatory effects, which demonstrated ability to prevent and to lessen the effects of RP attacks, and heal ischaemic digital lesions, by ameliorating vascular blood flow. Iloprost administration is currently performed in a hospital setting, poorly accepted by patients and with a heavy healthcare and economic burden. Nevertheless, due to the lack of relevant alternatives, other than bosentan and PDE-5 inhibitors like sildenafil, which have provided recent evidence of clinical efficacy in trials (3, 4), iloprost is widely used.

In the past years, portable devices for home infusion such as elastomeric pumps and small portable syringes have commonly been used in oncology and anesthesiology. They are safe, easy to use and well accepted by patients. These portable devices were used for iloprost infusion and were shown to be safe and well tolerated by patients affected by SSc or obstructive arterial disease in recently published studies (20-22). However, elastomeric pumps remain unauthorised devices for the administration of iloprost. Iloprost was demonstrated to remain stable for many hours (23) and long-term infusion devices were demonstrated to be well accepted and well tolerated by patients.

Our purpose was to use the small Infonde® portable syringe pump to administer iloprost at a low rate continuously, guaranteeing tolerance and few side effects, but maintaining the effects as previously described.

According to the minimum velocity of the pump, we choose to repeat the infusion for two consecutive days and repeat the cycle monthly for 6 months during the winter period. Our primary endpoints were safety and feasibility, because data concerning the clinical effects are already available in the literature and a study to evaluate efficacy would have required too many patients. Therefore, we calculated that an exploratory study to verify feasibility and safety, with an estimated drop out of less of 15%, would have required 20 patients. Unfortunately, we failed to enrol our estimated population because of exclusion criteria, which were too strict. In fact, we decided to exclude patients with concurrent vasodilator therapy like calcium-channel blockers and bosentan, to ensure safety and avoid hypotension risk, and this precautionary choice significantly limited enrolment. Nevertheless, we also reported the positive effects concerning reduction of severity and frequency of RP attacks and acral ulcers.

Our results indicate remarkable satisfaction with the use of the pump, not only by patients, but also nurses and physicians.

Iloprost home infusion with Infonde® pump allowed more regular drug administration and proved to be feasible as only one patient withdrew from the study due to poor tolerance, but this patient did not tolerate any alternative method of iloprost administration either.

The safety analysis has brought good results. There was a lower global incidence of side effects and a better tolerance compared to the traditional methods of infusion, consequent to the lower infusion speed and regular administration. However, a correct management of the pump and of the venous access as well as either adequate veins or a central venous line are necessary. Despite the limited number of cases, iloprost administration was confirmed to have positive effects on ischaemic ulcers and RP, as previously demonstrated in other studies (11-15), taking into account the influence of dropping temperatures during winter. It should be noted that the four patients who did not

present ulcers during the protocol, had experienced them in the previous years. Moreover, the worsening of clinical condition after the end of the infusions, despite the higher spring temperatures suggests the need to extend the duration of infusions. This confirms the importance of maintaining regular infusions, according to weather conditions. Concerning the global effects on RP, it is likely that the drug may influence duration and intensity over time rather than the number of attacks.

Finally, although there was not a significant improvement in the perception of quality of life, based on the HAQ scale, all the patients expressed a very positive judgment about the new infusion method and about the device, which was considered handy and easy to use. Further suitable studies, comparing the outpatient *versus* inpatient hospital infusion setting in randomised trials, will be necessary to guarantee at least the same efficacy and safety and allow the use of the pump to be fully available to any centre which deals with patients with SSc.

### Conclusion

The infusion of iloprost at home with the Infonde® portable syringe pump in the treatment of RP and ischaemic ulcers in patients with scleroderma is feasible, safe and effective, it also has advantages from the economic and organisational point of view. Because of the pilot design of our study, these results need to be confirmed in larger randomised trials.

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